PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	29 APR 2005
Applicant's or agent's file reference 701039-53521-PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/35874	28 October 2004 (28.10.2004)	29 October 2003 (29.10.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 39/395, 38/00 and US Cl.: 424/133.1, 145.1, 152.1, 158.1, 172.1; 514/2, 885

Applicant

CHILDREN'S MEDICAL CENTER CORPORATION

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. Claim 33 is an improper multiply dependent claim.

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 33 are so unclear that no meaningful opinion could be formed *(specify)*:

Claim 33 is an improper multiply dependent claim.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 5,13-17,23,35,37	YES
	Claims 1-4,6-12,18-22,24-32,34,36	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-32,34-37	NO
Industrial applicability (IA)	Claims 1-32,34-37	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-33,35-37 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Claims 1-4,6-12,18-20,22-27,34,36 lack novelty under PCT Article 33(2) as being anticipated by US Patent 5,547,959.
US Patent 5,547,959 discloses treatment of the allograft donor graft and recipient with rapamycin (a VEGF antagonist as per claim 36) to treat graft rejection (see columns 2-4). US Patent 5,547,959 discloses that the immunosuppressive agents CSA or FK-506 or prednisone can be used in combination with said treatment (see column 4). The graft can be a heart graft (see columns 3-4).

Claims 18-22,30,31 lack novelty under PCT Article 33(2) as being anticipated by WO 98/41344.
WO 98/41344 discloses the treatment of kidney allograft rejection using a humanized antibody against VEGF (see page 6, 7, 29).

Claims 1-32,34-37 lack an inventive step under PCT Article 33(3) as being obvious over US Patent 5,547,959 in view of WO 98/41344.
US Patent 5,547,959 discloses treatment of the allograft donor graft and recipient with rapamycin (a VEGF antagonist as per claim 36) to treat graft rejection (see columns 2-4). US Patent 5,547,959 discloses that the immunosuppressive agents CSA or FK-506 or prednisone can be used in combination with said treatment (see column 4). The graft can be a heart graft (see columns 3-4). WO 98/41344 discloses the treatment of kidney allograft rejection using a humanized antibody against VEGF (see page 6, 7, 29). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered the antiVEGF antibody to the recipient receiving the rapamycin treated graft because US Patent 5,547,959 discloses treatment of the allograft donor graft and recipient with rapamycin to treat graft rejection and that other immunosuppressive agents can be used in combination with said treatment whilst WO 98/41344 discloses the treatment of kidney allograft rejection using a humanized antibody against VEGF. The use of the immunosuppressive mycophenolate and its related derivatives is well known in the art for the treatment of graft rejection. Bevacizamab is a commercially available humanized antiVEGF antibody. PTK 787 is a commercially available art known VEGF inhibitor. The method could have been used with any graft donor.